Lung Cancer in Radon-Exposed Miners and Estimation of Risk From Indoor Exposure

*Jay H. Lubin, John D. Boice, Jr., Christer Edling, Richard W. Hornung, Geoffrey R. Howe, Emil Kunz, Robert A. Kusiak, Howard I. Morrison, Edward P. Radford, Jonathan M. Samet, Margot Tirmarche, Alistair Woodward, Shu Xiang Yao, Donald A. Pierce**

Background: **Radioactive radon is an inert gas that can migrate from soils and rocks and accumulate in enclosed areas, such as homes and underground mines. Studies of miners show that exposure to radon decay products causes lung cancer. Consequently, it is of public health interest to estimate accurately the consequences of daily, low-level exposure in homes to this known carcinogen. Epidemiologic studies of residential radon exposure are burdened by an inability to estimate exposure accurately, low total exposure, and subsequent small excess risks. As a result, the studies have been inconclusive to date. Estimates of the hazard posed by residential radon have been based on analyses of data on miners, with recent estimates based on a pooling of four occupational cohort studies of miners, including 360 lung cancer deaths.** ***Purpose:*** **To more fully describe the lung cancer risk in radon-exposed miners, we pooled original data from 11 studies of radon-exposed underground miners, conducted a comprehensive analysis, and developed models for estimating radon-associated lung cancer risk.** ***Methods:*** **We pooled original data from 11 cohort studies of radon-exposed underground miners, including 65 000 men and more than 2700 lung cancer deaths, and fit various relative risk (RR) regression models.** ***Results:*** **The RR relationship for cumulative radon progeny exposure was consistently linear in the range of miner exposures, suggesting that exposures at lower levels, such as in homes, would carry some risk. The exposure-response trend for never-smokers was threefold the trend for smokers, indicating a greater RR for exposure in never-smokers. The RR from exposure diminished with time since the exposure occurred. For equal total exposure, exposures of long duration (and low rate) were more harmful than exposures of short duration (and high** rate). Con***clusions:***

Exposure in miners is estimated in units of working-level months (WLM) *(15).* One working level (WL) equals any combination of radon progeny in 1 L of air that results in the ultimate emission of 13 0000 MeV of energy from alpha particles. WLM is a time-integrated exposure measure and is the product of time in working months (170 hours) and WLS. In terms of the International System of Units (SI units), 1 WLM corresponds to 2.08×10^{-5} J/m^3 x 170 hours = 3.5×10^{-3} J-hours/m^3. Indoor levels of Rn are measured in picocuries per liter (or becquerels per cubic meter). In a typical home, Rn concentration is about 1 pCi/L (or 37 Bq/m^3), which for Rn at 50% equivalent with its decay products results in a Rn progeny level of 0.005 WL, approximately 50-100 times lower than the lowest WL found in mines. In an average home, yearly exposure results in approximately 0.2 WLM or an approximate lifetime cumulative exposure of 10-20 WLM. Subjects residing for a lifetime in a home at the EPA action level of 4 pCi/L accumulate 40-80 WLM. Indoor concentrations vary widely between countries; in the United Kingdom, the mean concentration is about 0.5 pCi/L *(16),* while in Sweden the mean concentration is 2.6 pCi/L *(17).* Within countries, concentrations also vary widely; e.g., in the United States, the mean concentrations among states range from less than 1 pCi/L to more than 8 pCi/L, although less than 1% of homes exceed 8 pCi/L *(18).*

To more fully describe the lung cancer risk in Rn-exposed miners, we pooled original data from 11 studies *(4-14)* of Rn-exposed underground miners, conducted a comprehensive analysis, and developed models for estimating Rn-associated lung cancer risk. The studies included all published cohort studies with 40 or more lung cancer deaths and with exposure to Rn progeny estimated for individual miners (see Table 1). We analyzed data from more than 65 000 miners who accrued nearly 1.2 million person-years of observation and experienced more than 2700 lung cancer deaths. In contrast, current estimates by the U.S. Environmental Protection Agency (EPA) and others of the effect of radon progeny exposure for the United States are based on a model reported in 1988 by the Biological Effects of Ionizing Radiation (BEIR) IV Committee and derived using data from four miner cohorts with 360 lung cancer deaths *(2).*

Methods for Relative Risk Regression

In pooled data with several thousand lung cancer deaths, it is possible to examine more subtle effects than can be done in individual studies. The essence of such analysis consists of fitting regression-type models, with moderately few parameters, to raw death rates in thousands of cells of cross-classified data. Models for the relative risk (RR) of lung cancer are specified as a function of cumulative WLM and other factors.

Data on lung cancer cases and person-years of follow-up were summarized in a multiway table defined by categories of attained age, year, WLM, and other factors and analyzed as if cases in each cell were independent Poisson variates *(1,19,20).* A 5-year lag interval for WLM was assumed; for each year of follow-UP, exposure within 5 years did not affect lung cancer risk. The age-specific lung cancer rate, $r(x,z,w)$. was assumed to depend on cumulative WLM *(w).* a vector of covariates *(x)* that describes the background disease rate among nonexposed, and a vector of covariates *(z)* that modifies the exposure-response relationship. Components of x and z may be time independent (e.g., age at first employment) or time dependent (e.g., attained age and duration of exposure). The age-specific disease rate was modeled as

$$r(x,z,w) = r_0(x)\mathbf{RR}(z,w),$$

where the RR function, $RR(z,w,)$, multiplied the background disease rate $r_0(x)$. For pooled analysis, $r_0(x)$ included stratification parameters for categories of attained age, a measure of other mining exposures (China, Colorado, Ontario, New Mexico, and France), ethnicity (New Mexico), and cohort. There were 225 strata with nonzero person-years. Smoking data, available for only six cohorts. were analyzed separately.

Preliminary analyses revealed that the RR for each cohort was consistent with linearity in WLM. The only exception was the Colorado data that exhibited a downturn of the RRs at the highest exposures; for Colorado, data were restricted to exposures under 3200 WLM, a range in which the RR was consistent with linearity. The underlying basis for our analyses was the excess RR (ERR) model (model l), which is expressed as

$$\mathbf{RR}(w) = 1 + \beta w,$$

where β was the exposure–response trend parameter, specified as ERR/WLM.

Model 1 was used only for initial exploration of the data. With the large amount of data and the ability to evaluate subtle effects, the models actually developed for risk estimation took a more complicated form. Model 1 was generalized in two ways. First, the exposure-response β was permitted to vary by categories of one or more cofactors, e.g., β, β,$\beta\phi_{55-64}$and $\beta\phi >_{65}$, where $\phi >_{55\text{-}64}$and $\phi >_{65}$ represent modifiers of the ERR/WLM for attained ages 55-64 years and 65 years or older relative to ages younger than 55 years. Second, to assess effects of exposure occurring in various time intervals prior to lung cancer death. we assigned cumulative WLM to three exposure windows. For each year of follow-up, WLM was expressed as $w = w_{5\text{-}14} + w_{15\text{-}24} + w_{25+}$ where $w_{5\text{-}14}$, $w_{15\text{-}24}$, and w_{25+} were exposures received 5-14 years, 15-24 years, and 25 years or more prior to a given age, respectively, with exposures within 5 years assumed to be unrelated to lung cancer death. Model 1 was generalized as

$$\mathbf{RR}(w_{5\text{-}14},w_{15\text{-}24},w_{25+}) = 1 + \beta\,(w_{5\text{-}14} + \theta_2 w_{15\text{-}24} + \theta_3 w_{25+}),$$

with parameters $\theta_2$and $\theta_3$representing the relative effects of exposure in the time windows.

A summary ERR/WLM was computed as a weighted mean of 11 cohort-specific β estimates. The confidence interval (CI) was based on a random effects model and accounts for variability within and between cohorts. CIs for lifetime risk estimates and for attributable risks were based on a Taylor series expansion and the covariance matrix for the parameter estimates, with the variance of the summary ERR/WLM replaced by the random effects variance *(1).*

Results

Risk With Rn Progeny Exposure

The initial evaluation examined the similarity of the exposure–response relationship across the studies. The last two columns of Table I show estimates of β from fitting model 1 to each cohort. The ERR/WLMs ranged from 0.002 to 0.051, which corresponded to RRs at 100 WLM ranging from 1.2 to 6.1. The combined ERR/WLM was 0.0049 (95% CI = 0.002-0.010) or an RR at 100 WLM of 1.49. Except for the Radium Hill study for which the CI was entirely outside that of the combined ERR/WLM, most estimates were about 0.01 or less and varied about 10-fold.

For the pooled data, Fig. 1 shows RRs and 95% CIS for categories of WLM relative to zero exposure, plotted at the mean for the category, and the fitted model 1. Categories for WLM were 0, 1-24, 25-49, 50-74, 75-99, 100-199, 200-399, 400-799, 800-1599, and 1600 WLM and greater, with mean values 0.0, 11.3, 31.7, 69.0, 81.8, 144.5, 280.5, 512.8, 681.9, 1099.8, and 2408.8 WLM, respectively. The apparent nonlinearity above about 600 WLM was not a statistically significant departure from linearity. Under 600 WLM, a range that included 2075 lung cancer cases, the trend in the RRs was consistent with linearity (Fig. 1). Statistically significant RRs were observed for all categories above 50 WLM.

Table 1. Summary of study populations in pooled analysis and estimates of ERR/WLM

Study site (reference No.)	Type of mine	Person-years		Lung cancer deaths		WLM*	No. of years exposed*	ERR/WLM	95% CI
		Exposed	Non-exposed	Exposed	Non-exposed				
Yunnan Province, People's Republic of China (*4*)	Tin	135 357	39 985	936	44	277.4	12.9	0.0016	0.001-0.002
W. Bohemia, Czech Republic† (*5*)	Uranium	103 652	4216	656	5	198.7	7.3	0.0034	0.002-0.006
Colorado Plateau‡ (*6*)	Uranium	73 509	7403	292	2	595.7	4.0	0.0042	0.003-0.007
Ontario, Canada§ (*7*)	Uranium	319 701	61 017	282	2	30.8	3.0	0.0089	0.005-0.015
Newfoundland, Canada (*8*)	Fluorspar	35 029	13 713	112	6	367.3	4.8	0.0076	0.004-0.013
Malmberget, Sweden (*9*)	Iron	32 452	841	79	0	80.6	17.8	0.0095	0.001-0.041
Grants, New Mexico (*10*)	Uranium	46 797	12 152	68	1	110.3	7.4	0.0172	0.006-0.067
Beaverlodge, Canada (*11*)	Uranium	68 040	50 345	56	9	17.2	1.9	0.0221	0.009-0.056
Port Radium, Canada (*12*)	Uranium	30 454	22 222	39	18	242.8	3.2	0.0019	0.001-0.006
Radium Hill, Australia (*13*)	Uranium	25 549	26 301	32	22	7.6	1.1	0.0506	0.010-0.122
France (*14*)	Uranium	39 487	4556	45	0	68.7	13.2	0.0036	0.001-0.013
Combined‖		907 459	242 332	2597	109	158.0	5.7	0.0049	0.002-0.010¶

*Mean among Rn progeny-exposed miners.

†For historical reasons, the study is referred to in the text as the Czechoslovakia cohort, although it is now two independent countries, the Czech Republic and Slovakia. About 25% of the miners were of Slovak origin, and most later returned to Slovakia.

‡Totals exclude data above 3200 WLM, including 35 lung cancer cases.

§Study consisted of all uranium miners, including those with previous gold mining experience.

‖Totals adjusted for 115 workers (including 12 lung cancer case patients) who were included in both the New Mexico and Colorado cohorts.

¶Joint 95% CI based on random effects model.

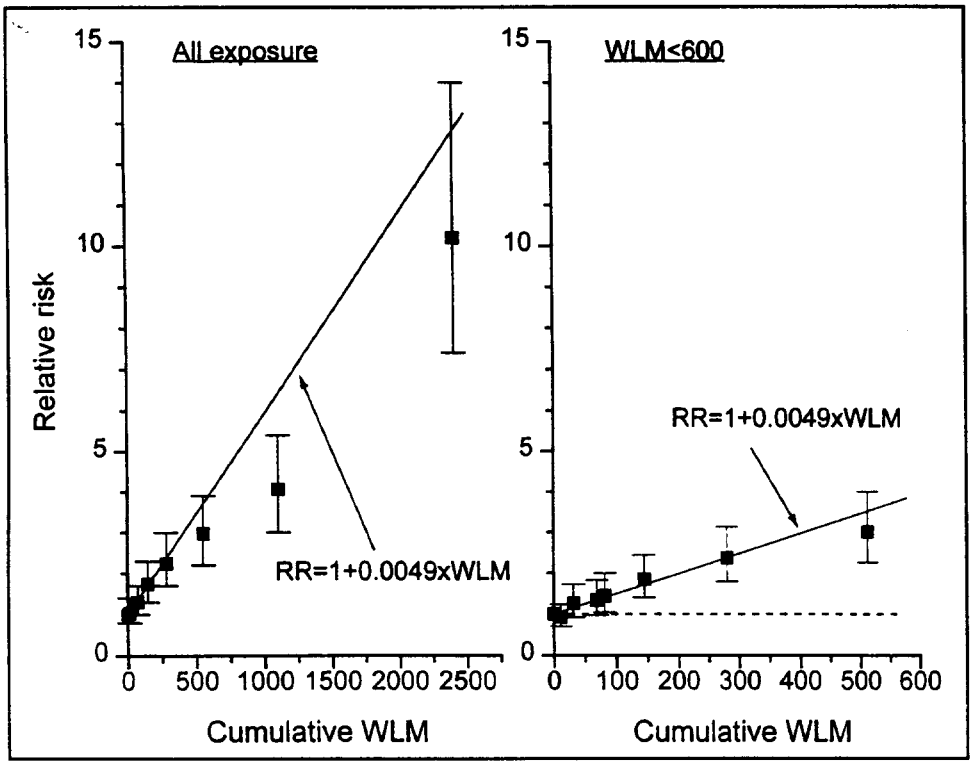

Fig. 1. RRs of lung cancer for categories of WLM and fitted exposure–response model for miner cohorts for all exposures and for exposures restricted to under 600 WLM. For all exposures, deviation from linearity was not statistically significant. Dash line shows an RR of 1. For residential Rn exposure, living 30 years in a home at 1 pCi/L and 4 pCi/L is equivalent to about 6 WLM and 24 WLM, respectively.

Table 2 summarizes findings for potential modifiers of the exposure–response relationship. The ERR/WLM varied significantly with several factors. declining with increasing age. time since last exposure. and time since exposure. but did not vary consistently with age at first exposure. The ERR/WLM increased with duration of exposure (or correspondingly, !ower exposure rate. This pattern, commonly referred to as an "inverse exposure rate" effect, indicates that, for equal total exposure, risks for underground miners were greater for exposures received at a low rate (and long duration) than for exposures received at a high rate (and short duration).

We also conducted analyses evaluating the consistency of the effects across the studies. Heterogenity of the ERR/WLIM persisted even after adjustment for the modification factors. while

[redacted]

Exposure to arsenic in mine dusts	Data from two cohorts. After adjustment, ERR/WLM declined from .006 to .002 for the China cohort and from .009 to .008 for the Ontario cohort.	Arsenic exposure may affect extrapolation of miner-based risk models to homes. Results need confirmation in other studies.
Previous mining experience	Data from three cohorts. Results mixed. After adjustment, ERR/WLM increased in the Colorado cohort and decreased in the New Mexico and France cohorts.	Interpretations are problematic, since type and extent of exposure at previous mines are uncertain and exposure likely occurred many years prior.

*Terminology indicates the direction of effect and not necessarily level of statistical significance.

the effects of the modification factors (attained age, time since exposure, exposure rate, and duration) on the ERR/WLM did not vary significantly by cohort.

Five cohorts had information on exposure to other potentially relevant factors. The China and Ontario studies had data on airborne arsenic in mines, and adjustment for arsenic exposure decreased the ERR/WLM estimates. The Colorado, New Mexico, and French cohorts had data on previous employment as miners. Except for the Colorado study, adjustment for previous mine employment reduced ERR/WLM estimates slightly.

Smoking and Rn Progeny Exposure

Because smoking is the most important cause of lung cancer, the joint effects of Rn progeny exposure and smoking have important implications for risk evaluation. If RRs for smoking and Rn progeny exposure are multiplicative, then the RR for Rn progeny exposure is the same in smokers and never-smokers, and, because the lung cancer rate is higher in smokers, the absolute increase in the lung cancer rate attributable to Rn progeny exposure is substantially greater in smokers. In contrast, if RRs for smoking and exposure are additive, then the absolute increase in lung cancer rate attributable to Rn progeny exposure is the same in smokers and never-smokers and, therefore, proportionally less in smokers.

Six cohorts had direct data on smoking *(4,6,8-10,13),* while a seventh study *(21)* had data from a related case-control study (Table 3). Data on tobacco consumption patterns had limited comparability among the studies because of differences in survey methodology. In the analysis of the six cohorts, joint effects of WLM and smoking were assessed using several approaches: One approach is shown here. Categories were defined for WLM *(w)* and a smoking-related variable *(s).* Age-adjusted RRs were computed for each cell of the cross-classification $(RR(w,s) = \Phi_{ws})$, designated as the "unrestricted" model, and compared with fitted RRs based on two restricted models, namely, the multiplicative model, $RR(w,s) = \Phi_w, \Phi_s$ and the additive model, $RR(w,s) = \Phi_w + \Phi_s, - 1$. In Table 4, significant *P* values indicate a poor fit of the model relative to the unrestricted model.

A consistent pattern for the joint WLM and smoking RRs did not emerge (Table 4). For each cohort, except Colorado, both the additive and the multiplicative models provided an adequate fit. For the Colorado study, additivity was rejected, while the multiplicative model was consistent with the data. Further analyses revealed that the joint association was compatible with a wide range of models, but it was most consistent with a model intermediate between an additive and multiplicative relationship. These analyses were burdened by small numbers of cases in several cohorts, which limited the power to discriminate among alternative models.

Rn Progeny Exposure Effects in Never-Smokers

Because of the high proportion of smokers among the miners, it has been suggested that the increasing risk with Rn progeny exposure may be primarily due to tobacco use; this is unlikely. Two studies *(22,23)* of never-smokers and light smokers have shown increased risk with exposure, although exposure–response trends could not be estimated. A study of never-smoking Colorado uranium miners *(22),* including 14 who died of lung cancer, reported a 13-fold greater risk compared with that for never-smoking U.S. veterans, and a study among Navajo men *(23),* who generally do not smoke or are light smokers,

[redacted]

Sweden	Type of product: duration, rate, and cessation of use	From random samples of [redacted] survey of pensioners and next-of-kin of deceased case patients.	[redacted] association. Best estimate was an intermediate association.
New Mexico	Cigarette use: duration, rate, and cessation	At time of physical examination at Grants Clinic. Data available through time of last examination.	Study had limited power to estimate joint association. Best estimate was an intermediate association.
Beaverlodge*	Detailed smoking history	From personal interviews with next-of-kin.	Study had limited power to estimate joint association, but results consistent with multiplicative model.
Radium Hill	Smoking status	From survey of cohort, started in 1984. Data on about half of cohort, including one never-smoking lung cancer case.	Analysis of joint effects not possible.

*Smoking results based on a case–control study of 46 lung cancer case patients and 93 matched control subjects.

found an excess lung cancer risk associated with employment at uranium mines.

In the pooled data, there were 2798 workers who were reported to be never-smokers; these data included 50493 person-years of follow-up and 64 lung cancer cases. RRs increased with WLM exposure for smokers and never-smokers (Fig. 2). Model 1 was fit separately to never-smokers and to smokers, with adjustment for cohort, attained age, ethnicity, and other miner exposures. The estimated ERR/WLM for never-smokers was 0.0103 (95% CI = 0.002-0.057), which is about threefold higher than the estimated 0.0034 (95% CI = 0.001-0.015) for smokers. The lower ERR/WLM for smokers is consistent with a submultiplicative joint association.

Assessment of Lung Cancer Risk From Exposure to Rn Progeny

Employing life-table methods and models from the pooled analysis. we assessed consequences of Rn progeny exposure by using two statistics: 1) the ratio of the lifetime risk of lung cancer with exposure *(R)* to the lifetime risk of lung cancer without exposure (R_o) (i.e., the lifetime RR of lung cancer. [LRR] = R/R_o; and 2) population attributable risk (AR) of lung cancer due to exposure (i.e., the proportion of all lung cancer deaths in a population due to exposure). In estimating LRR and AR for home exposures. we used 1985-1989 U.S. mortality rates as the referent disease rates for a nonexposed population. We adjusted the age-specific population lung cancer rates to retlect rates in smokers and never-smokers by assuming smoking RRs of 14.0 and 12.0 and proportions of smokers of 0.7 and 0.5 for males and females, respectively. Age started smoking was taken as 18 years.

[redacted]

either exposure duration (DUR) or exposure rate (WL). The model used for this article, the TSE/AGE/DUR model, is as follows:

$$RR(w, AGE, DUR) = 1 + \beta \times (w_{5\text{-}14} + \theta_2 w_{15\text{-}24} + \theta_3 w_{25+}) \times \phi_{AGE} \times \gamma_{DUR}$$

where $\beta = 0.0039$, $\theta_2 = 0.76$, $\theta_3 = 0.31$,

$$\phi_{age} = \begin{cases} 1.00 \text{ for age } <55 \\ 0.57 \text{ for } 55 \le \text{age } <65 \\ 0.34 \text{ for } 65 \le \text{age } <75 \end{cases} \qquad \gamma_{DUR} = \begin{cases} 1.00 \text{ for DUR } <5 \text{ y} \\ 3.17 \text{ for } 5 \le \text{DUR } <15 \text{ y} \\ 5.27 \text{ for } 15 \le \text{DUR } <25 \text{ y} \end{cases}$$

[redacted]

For indoor exposures, a factor, often called the F factor, is applied to account for dosimetry differences that result from dif-

Table 4. Interactions of WLM and smoking, with age-adjusted RRs under various unrestricted and restricted models*

Study	Model	Status	No. of case patients	WLM				P†
China				Cumulative WLM				
				<200	200-799	≥800		
	Unrestricted	Never-smoker	25	1.0	2.2	3.1		
		Ever-smoker	882	3.3	4.5	6.1		
	Multiplicative	Never-smoker		1.0	1.4	1.9		.64
		Ever-smoker		2.2	3.0	4.1		
	Additive	Never-smoker		1.0	2.1	3.8		.90
		Ever-smoker		3.4	4.6	6.1		
		Total No. of case patients	907	194	546	167		
Colorado				Cumulative WLM				
				<600	600-839	840-1599	≥1600	
	Unrestricted	Never-smoker	25	1.0	4.2	2.9	8.1	
		Ever-smoker	267	4.0	6.9	10.7	18.7	
	Multiplicative	Never-smoker		1.0	1.9	2.7	4.9	.58
		Ever-smoker		3.0	5.7	8.1	14.7	
	Additive	Never-smoker		1.0	4.4	7.1	15.8	.04
		Ever-smoker		4.9	8.3	11.0	19.7	
		Total No. of case patients	292	103	34	74	81	
Newfoundland				Cumulative WLM				
		Smoker: cigarettes/d		<400	400-1599	≥1600		
	Unrestricted	<20	9	1.0	1.6	7.8		
		≥20	16	0.9	3.7	9.1		
	Multiplicative	<20		1.0	3.0	9.4		.53
		≥20		1.4	4.2	13.2		
	Additive	<20		1.0	3.3	10.5		.67
		≥20		1.3	3.6	10.8		
		Total No. of case patients	25	5	8	12		
Sweden				Cumulative WLM				
				<50	50-149	≥150		
	Unrestricted	Never-smoker‡	24	1.0	1.3	4.7		
		Ever-smoker	27	1.9	4.7	13.2		
	Multiplicative	Never-smoker		1.0	1.8	5.9		.43
		Ever-smoker		3.0	5.4	17.7		
	Additive	Never-smoker		1.0	1.7	7.1		.31
		Ever-smoker		4.6	5.3	10.7		
		Total No. of case patients	51	6	19	26		
New Mexico				Cumulative WLM				
		Smoker: cigarettes/d		<200	200-399	≥400		
	Unrestricted	<20	35	1.0	1.9	8.1		
		≥20	17	1.2	5.0	2.7		
	Multiplicative	<20		1.0	2.6	6.2		.15
		≥20		1.2	3.1	7.4		
	Additive	<20		1.0	2.7	6.9		.11
		≥20		1.5	3.2	7.4		
		Total No. of case patients	52	18	17	17		

*For WLM (w) and smoking (s), the models are as follows: the unrestricted model $RR(w,s) = \phi_{w,s}$, with one RR for each cell; the multiplicative model $RR(w,s) = \phi_w\phi_s$ and the additive model $RR(w,s) = \phi_w + \phi_s - 1$.

†Test of fit for a model relative to the full model with one RR parameter for each cell. Significant P value indicates a poor fit relative to the full model.

‡For Swedish cohort, category includes exsmokers.

ferences in breathing rates, proportion of nasal versus oral breathing, aerosol size, and other factors between underground miners and persons living in homes *(15)*. The K factor, which compares the dose of alpha energy per WLM with target cells in the respiratory tract for an individual in the home with the dose–exposure ratio in miners, was assumed to be 0.8 for ages under 10 years and 0.7 otherwise.

LRR OF LUNG CANCER

In projecting risk of Rn exposure, previous investigators *(1,2,24,25)* have applied the same risk model for males and females and, within gender, to smokers and never-smokers, thereby assuming a multiplicative association for exposure and gender and, within gender, for exposure and smoking. The mul-

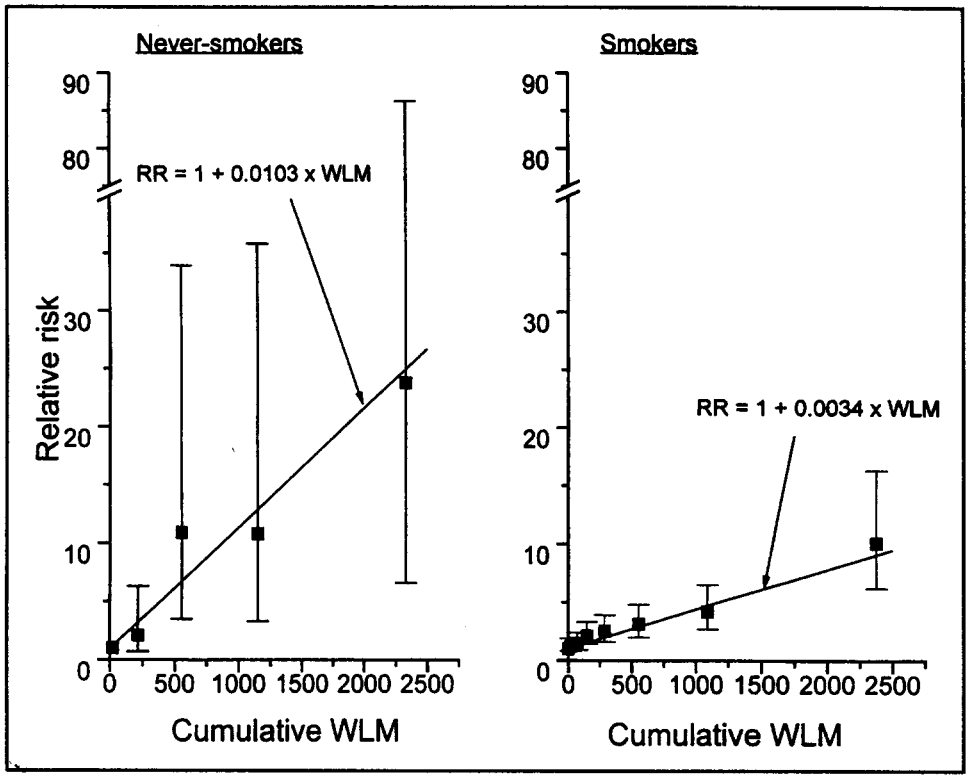

Fig. 2. RRs of lung cancer for categories of WLM and fitted exposure-response model for reported never-smokers and ever-smokers.

tiplicative assumption for gender is entirely speculative, as there are little data on the issue. For our calculations, we followed previous practice and used the same risk model for males and females and merely noted that, if the relationship for Rn exposure and gender was less than multiplicative, the computed values for the LRR and AR for females were underestimates. For Rn progeny exposure and smoking among male miners, a submultiplicative association was most consistent with the data. This implied that risk estimates that use the usual approach of applying the same model to smokers and never-smokers are likely too large for smokers and too small for never-smokers. In a new approach, we made an ad hoc modification to the overall risk models by the use of results of analyses within subgroups of smoking and never-smoking miners. The overall ERR/WLM was estimated as 0.0103 for never-smokers, 0.0034 for smokers, and 0.0037 if smoking status was ignored. Therefore, the proportional effect of smoking on the ERR/WLM was 0.9 (0.0034/0.0037) for smokers and 3.0 (0.0103/0.0037) for never-smokers. We used these results to modify the TSE/AGE/DUR model; the β value of 0.0039 was reduced to 0.0035 for smokers and was increased to 0.0117 for nonsmokers, while the other parameter estimates remained unchanged *(26)*.

Fig. 3 shows LRRs for a lifetime exposure at a constant rate for female smokers and female never-smokers. LRRs for the TSE/AGE/DUR and BEIR IV models were quite similar; for lifetime exposure at 4 pCi/L, LRR estimates for female smokers were 1.4 and 1.3, respectively; at 8 pCi/L, the LRR estimates were 1.7 and 1.6, respectively. Estimates diverge only at very high concentration levels. CIS for the excess LRR are about a factor of 2.0-2.5; i.e., LRR-1 is multiplied and divided by this amount. It is estimated that about 5%-10% of U.S. homes exceed 4 pCi/L *(27)*, corresponding to a Rn progeny concentration of approximately 0.02 WL, which is about one tenth the lowest WL in the miner data.

Fig. 4 shows LRRs by WL for occupational-like exposures starting at age 25 years and continuing for 5, 10, and 20 years' duration, assuming 170 hours per working month and a 2000-hour working year. A miner exposed at one WL accumulates 11.8 WLM each year. Current regulatory limits for mines specify a Rn progeny ceiling of 1.0 WL and a yearly exposure maximum of 4 WLM. LRRs based on the TSE/AGE/DUR model were generally below those based on the BEIR IV model.

AR of Lung Cancer

The distribution of Rn concentrations in single-family homes is highly skewed, with about 20% of U.S. homes above 2 pCi/L and 5%-10% above 4 pCi/L, and this distribution is approximated by a log-normal distribution with a geometric mean of 0.9 pCi/L and a geometric standard deviation of 2.84 *(27)*. With the use of this distribution, Fig. 5 shows ARs for the United States based on the TSE/AGE/DUR model. Overall, ARs were about 10% for males and 12% for females, slightly greater than the 9% and 11% estimated, respectively, with the BEIR IV model; however, the CIS were wide and overlapped considerably. For males and females, ARs were 10% and 12% for smokers and 28% and 3l% for never-smokers, respectively.

Approximately 149 000 individuals, 93 000 men and 56 000 women, died of lung cancer in the United States in 1993 *(28)*. We assumed that 70% of the deaths (65 100 males and 39 200 females) occur among residents of single-family dwellings, and 85% of these deaths (55 300 males and 33 300 females) occur among current and former smokers. Assuming an AR of 1l% for smokers and of 30% for never-smokers, 14400 lung cancer

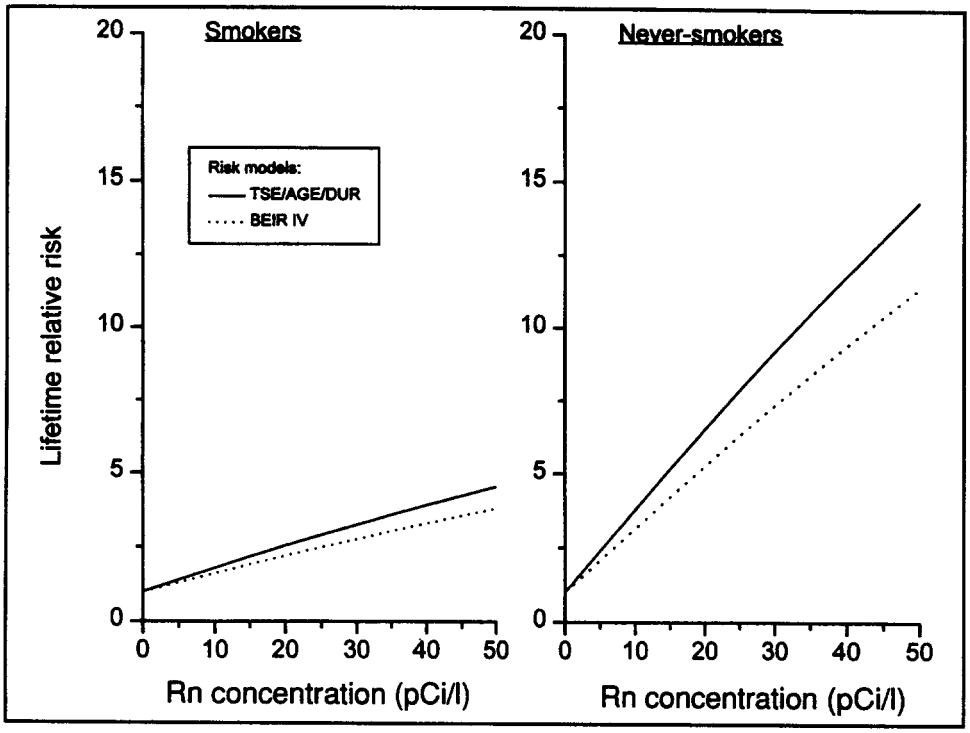

Fig. 3. Estimated LRR of lung cancer for females for lifetime exposure at a constant exposure rate forever-smokers and never-smokers.

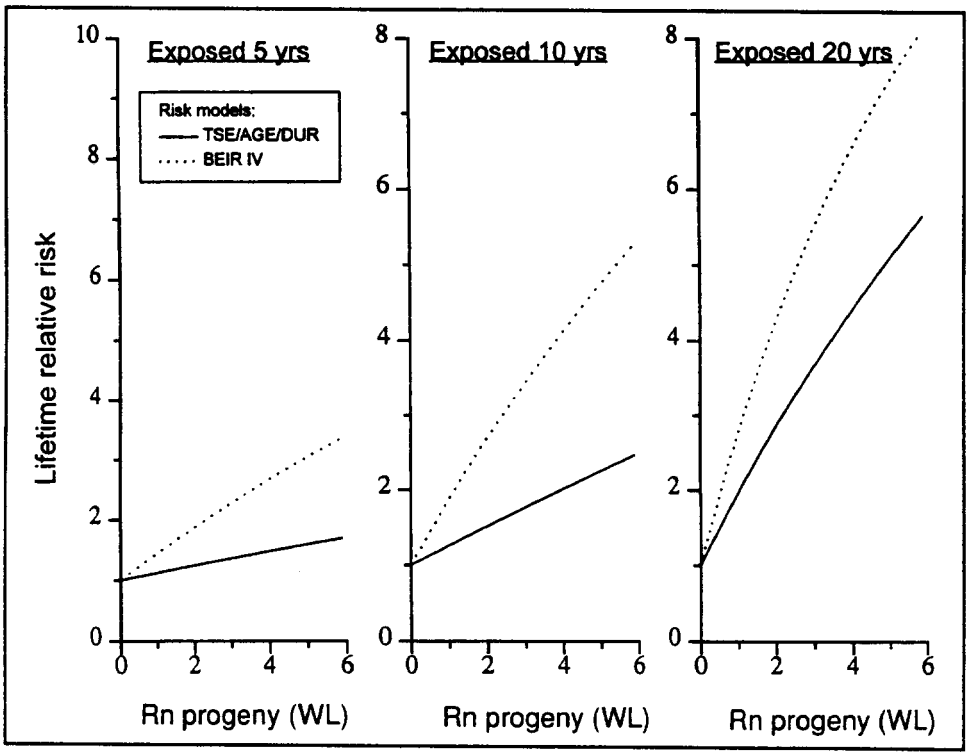

Fig. 4. Estimated LRR for males for exposures starting at age 25 years and continuing for 5, 10, and 20 years at a constant exposure rate.

deaths per year in the United States may be attributable to indoor Rn (or 10% of all lung cancer deaths), about 4700 among never-smokers and 9700 among smokers (Fig. 5).

The AR estimates the proportion of lung cancer deaths that may be reduced by "elimination" of Rn in homes, A more realistic characterization is "effective" AR by use of a plausible control scenario, such as the reduction in all homes of levels of Rn above 4 pCi/L to under 4 pCi/L. The mitigation of levels in all homes above 4 pCi/L results in an effective AR of about one fourth to one third the overall AR or about 2%-4% of total lung cancer deaths.

Rn concentrations in multifamily dwellings are not well characterized, but they may be twice the background levels or around 0.4 pCi/L *(29)*. Among the estimated 45 000 lung cancer deaths in residents of multifamily housing, Rn progeny exposure may account for several hundred lung cancer deaths.

Finally, underground miners have generally endured the highest Rn progeny exposures. In the pooled data, the fitted

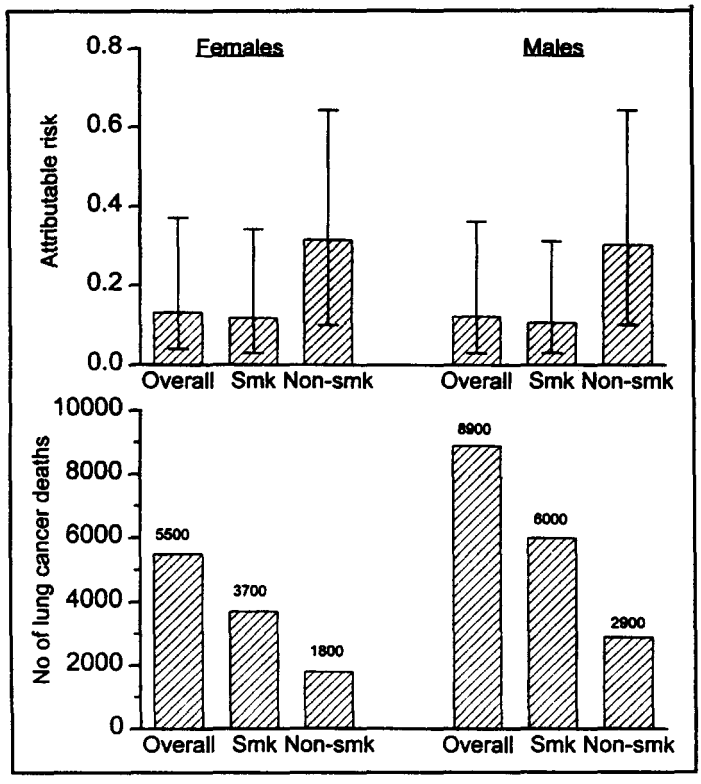

Fig. 5. AR of lung cancer in the United States and estimated number of lung cancer deaths per year attributable to residential radon progeny exposure.

models attribute 40% of lung cancer deaths among the miners to WLM exposure. Accounting for smoking, 70% of the lung cancer deaths among never-smokers, in contrast to 39% among smokers, may be due to exposure.

Discussion

The evidence for the carcinogenicity of Rn progeny exposure from the miner studies is unequivocal. Applying miner-based models to residences in the United States suggests that residential Rn may present a substantial public health problem, possibly responsible for 15 000 lung cancer deaths each year. This estimate is subject to the diverse uncertainties inherent in extrapolating risks estimated from studies of male, underground miners to the general population. We have not attempted to bound our estimate for the general population by these uncertainties, and the 95% CIS of 6000-36 000 are only a measure of statistical precision. Adjustment for other carcinogens that may contaminate mines reduced the Rn-related lung cancer risk and suggests the need for caution in generalizing these risk estimates to nonmining exposures.

The large amount of pooled data facilitated assessment of several potential modifiers of the exposure–response relationship. There has been concern that increased sensitivity of children to exposures may enhance risk of lung cancer in adulthood *(24)*. Only limited data in the pooled analysis were available to address the issue. Of 2585 lung cancer deaths among exposed miners, only the China study had cases among miners first exposed under age 15 years (522 cases or 20%), while nine of 11 studies had 629 (24%) cases among miners first exposed between ages 15 years and 24 years, including 299 cases from the China study. The analysis revealed no consistent modification of the ERR/WLM by age at first exposure across the cohorts. Thus, any enhancement of lung cancer risk from exposure at young ages would likely be slight, and lifetime risks would be balanced by the declining effect of time since exposure.

The air in a mine can be contaminated by known or suspect lung carcinogens, such as arsenic *(30)*, silica *(31)*, and diesel exhaust *(32)*, and by potential lung irritants, such as mine dusts, which may potentate cellular proliferation in lung epitheliums or slow clearance rates of Rn progeny and thereby increase dose *(15)*. Although the models were adjusted for available information on concomitant exposures, data on arsenic were limited to two cohorts, while three cohorts had only nonspecific data on such exposures. Appropriate adjustment for concomitant exposures was problematic, since the other exposures were potentially correlated with WLM, and independent effects may not be separable. It should be emphasized, however, that risks with Rn progeny exposure were found in a variety of mines, many of which had low levels of arsenic and other potential carcinogens. Nevertheless, the lack of detailed information on other mine exposures is an important gap in existing miner data.

The inverse exposure rate effect could be interpreted as implying that miner-based models underestimate risk in homes, where exposure rates are generally lower than in mines. In a conceptual model based on experimental findings, however, the effect is attributed to the consequence of multiple traversals of a cell by alpha particles and the process of cell cycling *(33)*, and it has been postulated that the inverse exposure rate effect diminishes at low total exposure, attributable to the low probability of multiple traversals. In contrast, arguments have been advanced suggesting that miner-based models may overestimate risk. While large doses of radiation are capable of inducing the required cellular changes for carcinogenesis, low doses may cause only a few of the required changes, resulting in a sublinear exposure–response relationship *(34)*. In addition, in vitro studies *(34)* indicated that at low exposure rates cells can repair alpha particle-induced chromosomal damage, resulting in less effect with protracted exposure. Thus, there remains substantial uncertainty in the extrapolation of the effects of exposure rates to the levels found in the home environment.

The ERR/WLM decreased with time since exposure, with the most remote exposure window being 25 or more years since exposure. Because of the limitations of the miner data, effects of exposures 35 years or more ago are not well estimated. If the effect of temporally remote exposures eventually disappears, then our projections may overestimate risk in homes. For example, if the w_{25+} time window in the TSE/AGE/DUR model were limited to 25-35 years with no excess risk thereafter, then, by using the same model parameters, AR would be about 25% lower. The decline in risk with time since exposure lends indirect support to the inference that control of indoor radon may be beneficial and, in the long term, reduce lung cancer risk.

Exposure estimates for all cohorts are likely affected by errors (random and systematic). Early measurements in the Colorado *(35)* and New Mexico *(36)* mines were motivated by regulatory concerns. and the WLM based on these measurements may be

too high. WLM for some Port Radium miners were underestimates because of lost work records prior to 1940 *(12)*. There is an indication that WLM may be underestimated for the Beaverlodge cohort *(37)*. Other cohorts undoubtedly have similar limitations, although perhaps of differing degrees. The magnitude of errors and their influence on modeling are difficult to evaluate without comparative data, which, in many cases, do not exist.

In summary, the predominant source of exposure in the general population to ionizing radiation is radon, which is inhaled daily by everyone. In the pooled miner data, radon progeny exposure had substantial consequences, responsible for perhaps 40% of all lung cancer deaths. Models developed from these data predict that as much as 10% of all lung cancer deaths in the United States may be due to indoor radon. However, because most homes have low radon levels, perhaps 2%-4% of lung cancer deaths may actually be preventable with present technology for radon measurement and control. Because of dissimilarities between typical exposures of the population and of underground miners in the epidemiologic studies, estimates of risk at the low levels experienced in the home are subject to substantial uncertainty. Nevertheless, for those few homes with very high levels, there is no question that remedial action should be taken; as a result, lung cancer risk would be lowered.

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Notes

The Czech study was initiated and led by Dr. Josef Ševc until his death in 1991. Current collaborators include Drs. Ladislav Tomášek. Emil Kunz, Josef Thomas, and Tomáš Müller from the National Institute of Public Health, and Dr. Václav Placek from the Institute of Industrial Hygiene in Uranium Industry of the Ministry of Health. The Canadian miner studies were supported by the Canadian Atomic Energy Control Board. and access to the death records at the National Centre for Health Information at statistics Canada was granted by the Registrar General of each province and territory in Canada, The Ontario study was also supported by the Workers' Compensation Board of Ontario and the Ontario Ministry of Labour. Co-investigators for the .Newfoundland project include Dr. D. Wigle and Mr. R. Semenciw, Dr. Samet was supported by grant DE-FG04-90ER60950 from the Office of Energy Research, U.S. Department of